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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,665	04/06/2000	Douglas Cines	9596-67U1	9220

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1653	11

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/544,665	Applicant(s) CINES ET AL.	
	Examiner Anish Gupta	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-10 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of Group I claims 1-10 and 17-20, with the elected species of EEIIMD in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims state a method of affecting a biological process. However, it is unclear how the biological process is affected. That is, is there an inhibition or promotion of the biological process. Since it is unclear what affect is to be observed, the claims are indefinite.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the peptide EEIIMD and SGTVASSSTAVIVSARSAPEEIIMD for inhibiting PAI-1- dependent adhesion of a cell , does not reasonably provide enablement for any peptide comprising EEIIMD, beyond SGTVASSSTAVIVSARSAPEEIIMD, and affecting biological process such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion and metastasis, and atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to enable the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to peptides, such as EEIIMD that facilitate the binding of scuPA to LM-TK$^-$ cells. The peptide EEIMD is a competitive inhibitor of PAI-1 biding to tcuPA.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(2) The state of the prior art and (4) The predictability or unpredictability of the art

As with all peptides, activity is based on the 3-dimensional structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. It is known in the art that the three dimensional structure of the peptide cannot be based on structure alone. For example, in peptide chemistry Ngo et al. teach that for proteins and peptides, a " 'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from its amino acid alone (see page 492 in Ngo et al.). Thus, activity of a given peptide can not be based on its structure alone. Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

Moreover, with respect to angiogenesis, the art indicates that inhibition is complex. The Mayo clinic reference discloses that many crucial question need to be asked about potential anti-angiogenic agents such as: what are the appropriate regimens, methods of administrations and doses and who should take them and when since it has been speculated that pregnant women and

people with healing wounds should avoid known anti-angiogenic drugs such as angiostatin or endostatin. The art recognizes other complications associated with angiogenesis. These include that all new vessels are not necessarily the same. "Blood vessels in the retina induced as a result of diabetic retinopathy may be different from those in other parts of the eye, such as the choroid or the iris." (See page 3 of Black). Further, tumor angiogenesis, wound angiogenesis, and eye angiogenesis involve different mechanism due to the different proteins involved in capillary formations in wounds and tumors (see page 4 of Black).

(5) The breadth of the claims

The method claims are drawn a method of affecting a biological process, such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion and metastasis, and atherosclerosis by the administration of the peptide of claim 1. The method claims also include method of inhibiting PAI-1-dependent adhesion of cells to a tissue of a mammals.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

The specification sets forth some insight with respect to the activity of the EEIIMD and REIIMD of promoting scuPA binding to LM-TK- cells and the effects of uPA mediated fibrinolysis. However, the specification fails to provide any guidance as to the effects of the peptide on tumors cell invasions, angiogenesis, ovulation, organogenesis, inflammation, and atherosclerosis. The specification concludes that such disorders would be treated since PAI-1

plays an important role in regulating these disorders, especially tumor cell adhesion and tumor metastasis. However the specification fails to provide any assay methodology that would give some credence to the implication set forth in the specification. The specification fails to provide guidance as to which type of tumors could be controlled by the peptide.

The Board of Appeals has held *Ex parte Sudilovsky*, that a disclosure was non-enabling since:

> "[t]he specification, though highly detailed, is devoted solely to a description of compounds stated to be known ACE inhibitors. The remainder of the specification is directed to how to make tablets and solutions for injection. Any disclosure regarding utility is confined to broad allegations and suggestions without substantiating working example. As stated in *In re Glass*, 492 F.2d 1228, 181 USPQ 31, 35 (CCPA 1974), 'the strong feeling one gets from reading the entire specification is that either appellant did not have possession of the details of a single operative process or, if he did, he chose not to divulge them.'"

Ex parte Sudilovsky, 21 U.S.P.Q2d 1702 (BPAI 1991). Similarly, the disclosure of the instant application, with regard to the biological activity, is confined to broad allegations and suggestions without substantiating working examples. Although working examples are not necessary in the specification, lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *In re Novak*, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) 4; *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). In this case, the disclosure has not provided evidence of record of a single

compound that would affecting a biological process, such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion and metastasis, and atherosclerosis. .

Moreover, the specification does provide guidance as to what amino acids sequences would be active beyond the two specific sequence disclosed, namely EEIIMD and REIIMD. It has been established in the art that one can not readily determine the effects of substitutions of amino acids to the native sequence based on structure alone. Again, Ngo et al. teach that for proteins and peptides, a " 'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from its amino acid alone (see page 492 in Ngo et al.). Thus, activity of a given peptide can not be based on its structure alone. Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(8) The quantity of experimentation necessary

Since, the art indicates a level of unpredictability in determining activity of a peptide based on structure alone one would be burdened with undue experimentation do practice the claimed invention for the reasons stated above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 5-6, 8, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Pannekoek.

The claims are drawn to a peptide comprising the sequence EEIIMD and methods of using said peptides.

The reference teach the sequence SGTVASSSTAVIVSARSAPEEIIMD, also referred to as PAI-1 P1-P1'AT3, that can be used in fibrinolytic/thrombolytic therapy (see page 17, lines 31-31). Note that the peptide reads on the claimed invention since contains the sequence EEIIMD, corresponding to the X1 correspond to the peptide SGTVASSSTAVIVSARSAP. The reference further teaches that the peptide inhibits thrombin in the absence or presence of vitronectin. Thus the peptide affects a biological process and prevents PAI-1 depended adhesion. Thus the reference anticipates the claims.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low,

can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

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